7-BENZYL-4-(2-METHYLBENZYL)-2,4,6,7,8,9-HEXAHYDROIMIDAZO [1,2-A]PYRIDO[3,4-E]PYRIMIDIN-5(1H)-ONE, ANALOGS AND SALTS THEREOF AND THEIR USE IN THERAPY

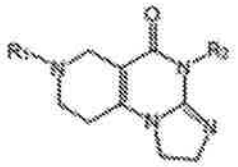
BACKGROUND OF THE INVENTION

[0001] TNF-related apoptosis-inducing ligand (TRAIL; Apo2L) is an endogenous protein that selectively induces apoptosis in cancer cells. TRAIL is a powerful inducer of apoptosis in a wide range of human cancer cell lines via pro-apoptotic death receptor 4 (DR4; TRAIL-R1) and death receptor 5 (DR5; TRAIL-R2) at the cell surface through engagement of the extrinsic or intrinsic apoptotic pathways. TRAIL plays a direct role in tumor suppression during immune surveillance but this anti-tumor mechanism is lost during the disease progression. The ability of TRAIL to initiate apoptosis selectively in cancer cells has led to ongoing clinical trials with administration of recombinant TRAIL and the longer-lived TRAIL-agonist antibodies targeting either of its two pro-apoptotic death receptors.

[0002] Despite its potency, recombinant TRAIL has efficacy-limiting properties such as short serum half-life, stability, cost, and delivery. Delivery of recombinant TRAIL or TRAIL-agonist antibodies to the brain is limited by inability of recombinant TRAIL and TRAIL-agonist antibodies to cross the blood-brain barrier. Accordingly, there is a continuing need for anti-cancer compositions and methods.

BRIEF SUMMARY OF THE INVENTION

[0003] In one aspect, provided herein are compounds of formula (**10**):



(10)

, wherein R_1 and R_2 independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl, alkoxycarbonyl, aralkoxy, aralkylthio, and acyl, radicals, wherein when R_1 represents CH_2Ph, R_2 does not represent CH_2-((2-CH_3)-Ph). In some embodiments, R_1 and R_2 are independently selected from the group consisting of H, C_{1-4}alkyl, C_{1-4}alkylphenyl, C_{1-4}alkylphenylketone, C_{1-4}benzyl-piperazine, C_{1-4}alkylthienyl, C_{1-4}alkylpyridinyl, C_{1-4}alkylisoxazolidinyl, C_{1-4}alkylmorpholinyl, C_{1-4}alkylthiazolyl, and C_{1-4}alkylpyrazinyl wherein C_{1-4}alkyl, C_{1-4}alkylphenyl, C_{1-4}alkylphenylketone, C_{1-4}benzyl-piperazine, C_{1-4}alkylthienyl, C_{1-4}alkylpyridinyl, C_{1-4}alkylisoxazolidinyl,